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Characteristics, management, and outcomes of patients with infectious encephalitis requiring intensive care: a prospective multicentre observational study

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Conflict of interest

None to declare

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PF: Formal analysis, Validation, Investigation, Roles/Writing - original draft

AM: Formal analysis, Validation, Investigation, Methodology; Conceptualization; Data curation; Funding acquisition; review & editing

JPS: Validation, Investigation, Methodology; Conceptualization; Data curation; Funding acquisition; review & editing

PT: Validation, Investigation, Conceptualization; Data curation; review & editing, Supervision

Abstract

Purpose: Infectious encephalitis (IE) is a severe disease which requires intensive care unit (ICU) admission in up to 50% of cases. We aimed to describe characteristics, management and outcomes of IE patients who required ICU admission.

Materials and Methods: Ancillary study focusing on patients with ICU admission within the ENCEIF cohort, a French prospective observational multicentre study. The primary criteria for outcome was the functional status at hospital discharge, categorized using the Glasgow outcome scale (GOS). Logistic regression model was used to identify risk factors for poor outcome, defined as a GOS ≤ 3 .

Results: We enrolled 198 ICU patients with IE. HSV was the primary cause (n=72, 36% of all IE, 53% of IE with microbiological documentation). Fifty-two patients (26%) had poor outcome at hospital discharge, including 22 deaths (11%). Immunodeficiency, supratentorial focal signs on admission, lower cerebrospinal fluid (CSF) white cells count ($<75/\text{mm}^3$), abnormal brain imaging, and time from symptoms onset to acyclovir start >2 days were independent predictors of poor outcome.

Conclusion: HSV is the primary cause of IE requiring ICU admission. IE patients admitted in ICU have a poor prognosis with 11% of in-hospital mortality and 15% of severe disabilities in survivors at discharge.

Keywords

Encephalitis, intensive care unit, Herpes simplex virus, functional outcome, frailty

Introduction

Infectious encephalitis (IE) is a severe disease with an incidence recently estimated as between 1.9 and 7.4 cases/year/100,000 inhabitants in developed countries [1,2]. Most cohort studies found that almost 50% of these patients require Intensive care unit (ICU) admission. So far, only retrospective studies, with limited sample size, or restricted to single pathogens (primarily herpes simplex encephalitis), have focused on IE requiring ICU admission [3–6]. Elevated body temperature on admission, extensive lesions on brain magnetic resonance imaging (MRI) and thrombocytopenia have been associated with poor outcome [3,7–9]. A better knowledge of characteristics of IE patients who require ICU admission might help to improve ICU management, particularly the decision of ICU admission, and the use specific treatment [10,11].

We aimed to decipher the characteristics of patients requiring ICU admission, their management, and the factors associated with poor functional outcome at hospital discharge.

Material and Methods

The ENCEIF cohort was a prospective multicentre observational study among 62 hospitals across France that enrolled all consecutive adult patients diagnosed with IE, according to the case definition of the International Encephalitis Consortium[12] from January 2016 to December 2019 [13]. Briefly, acute encephalitis was defined as neurologic symptoms of acute onset, for more than 24 h, with at least two of the following signs: fever $\geq 38^{\circ}\text{C}$, seizure, recent focal neurologic symptoms, cerebrospinal fluid (CSF) white cells count $\geq 5/\text{mm}^3$, inflammatory brain lesion on imaging, and suggestive abnormalities on electro-encephalogram (EEG). Encephalitis of unknown origin was defined using those criteria, with no identification of the pathogen involved, and after non-infectious causes have been ruled out, including autoimmune encephalitis. Diagnostic workout and management were left to the discretion of the physicians, although ENCEIF investigators were encouraged to follow the French guidelines that had been communicated in the national conferences of infectious diseases, and intensive care medicine, before the study started [14].

Data were collected on a standardized questionnaire and computerized using a secure, web-based application Voozadoo (Epiconcept©, Paris). In accordance with French regulation, the ENCEIF study protocol, an observational study, was reviewed and approved by the national ethics committee (Comite consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé CCTIRS): authorization n°14.725bis, on the 11th February 2015. Written consent was waived but we obtained informed non-opposition for the use of routine care medical data from all patients or from their close relatives. No human experimentation was carried out within the study, and no drug or medical device, or care protocol were tested. As for the protection

of medical confidentiality, the study was authorized by the French commission for data protection (Commission Nationale Informatique et Liberte, authorization n° 915148 on the 22th October 2015). This manuscript follows the STROBE statement for reporting cohort studies.

We performed a new ancillary study within the ENCEIF cohort, after those focusing on elderly patients and travellers[15,16]. Here, our aim was i) to compare non ICU and ICU patients regarding comorbidities and aetiologies, ii) to describe characteristics, management and outcomes of IE patients who required ICU admission and iii) to identify risk factors for poor outcome at hospital discharge among IE who required ICU admission. The primary criteria for outcome was the functional status at discharge, assessed using the Glasgow outcome scale (GOS) [17]. The GOS score ranges from 1 (death), to 5 (good recovery with return to baseline health status, i.e. before the IE episode, without consequence on daily living activities). Poor outcome was defined as a $GOS \leq 3$ at hospital discharge.

Statistical analyses were performed using the R 4.0.5 software. Categorical variables were described as numbers and percentages, and quantitative variables as medians and interquartile range. Categorical variables were compared by chi-square or Fisher's exact test, and continuous variables were compared by Mann Whitney test. Univariate and multivariate analyses were used to identify predictors of poor outcome at discharge, expressed as odds ratio (OR) and 95% confidence intervals (95%CI) using logistic regression model. Log linearity of continuous variables was tested and, if necessary, variables were categorized according to clinically relevant cut-offs or at median values. Baseline variables included in the multivariate model were those with $P < 0.20$ in univariate analysis. The final model was computed by a step-by-step backwise regression, using the Akaike criterion. Logistic models were evaluated for calibration with the Hosmer-Lemeshow test. Kaplan-Meier overall survival curves until day 180 were computed and compared with log-rank test. All tests were two sided and a P value < 0.05 was considered significant.

Results

Among the 494 patients enrolled in the ENCEIF study, 206 (42%) required ICU admission [13]. Eight patients were excluded because of missing data regarding GOS, resulting in 198 patients in the ICU cohort.

Comparison between non ICU and ICU patients (Table 1)

Patients who required ICU admission were younger than patients without ICU admission, with a median age of 63 years [42-74] vs. 67 years [51-75], $P=0.032$. The proportion of cases due to HSV was higher in ICU patients (36%

of all IE, 53% of IE with microbiological documentation), than in patients who did not require ICU admission (20%, and 31%, respectively), $P<0.001$. Of note, among all HSV encephalitis patients in the cohort, 72/129 (56%) required ICU admission. Altogether, HSV, VZV, and *Listeria monocytogenes* were the aetiology in 104/198 (53%) of ICU IE, versus 112/288 (39%) of IE with no ICU admission, $P<0.001$. Arboviruses were less common in IE requiring ICU admission although they represented an important proportion of patients in the whole cohort: 4/198 (2%) vs. 30/288 (10%) in non ICU patients, $P=0.001$.

Characteristics and management of patients who required ICU admission

The baseline characteristics of IE in patients who required ICU admission are reported in table 2. In ICU patients, time from onset of neurological signs to hospital admission was 2 days [0-3]. Treatment and outcomes are detailed in table 3. Of note, a potentially active anti-infective treatment was available for 126/137 (92%) of ICU IE with an identified causative agent. Invasive mechanical ventilation was required for 111/197 (56%), for a median duration of 7 days [4-14]. Seizures during ICU stay were reported in 49/198 (37%) of cases. Incidence of in-ICU acquired infection was high (25.5/1000 patients-days at risk), without difference between patients with good or poor outcome ($P=0.763$). Median ICU length-of-stay was 6 days [4-14] and hospital length-of-stay was 25 days [16-39].

Prognostic factors in patients who required ICU admission

Finally, 52 patients (26%) had poor outcome at hospital discharge, including severe deficits (n=28, 14%), in-hospital death (n=22, 11%), and vegetative status (n=2, 1%). Ninety patients (45%) had good recovery, and 56 (28%) had minor disability. HSV encephalitis was associated with poor outcome in univariate analysis ($P<0.001$) but not in multivariate analysis. There was no difference in clinical characteristics between patients with good or poor outcome, except for supratentorial ($P=0.009$), and respiratory signs ($P=0.017$). Median CSF white cells count was lower among patients with poor outcomes (30/mm³ [9-151] vs. 103/mm³ [24-349] in those with good outcomes, $P=0.006$). Abnormal findings on brain imaging ($P<0.001$), and cause of IE ($P=0.002$), were also associated with poor outcomes. In the overall cohort of IE patients who required ICU admission, time from symptoms onset to acyclovir start was longer in patients with poor outcome ($P=0.029$). For HSV and VZV encephalitis, time from symptoms onset to acyclovir initiation were 4 days [2-6] in patients with poor outcome, and 2 days [1-4] in patients with good outcome, $P<0.001$. Variables independently associated with poor outcome in multivariable logistic regression analysis were immunodeficiency, supratentorial focal signs, lower CSF white cells count (<75/mm³), abnormal brain imaging, and time from symptoms onset to acyclovir start >2 days, table

4. The model goodness-of-fit was 0.953. When aetiologies were forced in this model, categorized as HSV encephalitis or IE due to a causative agent different from HSV while reference was the group with no microbiological documentation, lower CSF white cells count remained associated with poor outcome ($P<0.001$). Survival rate until 180 days was lower in patients with low CSF white cells count (log-rank test, $P=0.01$), figure 1.

Discussion

In this large multicentre prospective cohort of IE patients, main results were i) comparing non ICU and ICU patients, HSV is the primary cause of IE requiring ICU admission, representing >50% of cases with an identified causative agent, which is nearly twice more than in non ICU patients, but HSV was not independently associated with poor outcome; ii) focusing on ICU patients, 26% of patients with IE have a poor outcome at hospital discharge; iii) immunodeficiency, supratentorial focal signs on admission, lower CSF white cells count, abnormal brain imaging, and time from symptoms onset to acyclovir start >2 days were independent predictors of poor outcome in ICU patients.

Age difference between ICU and non ICU patients could be linked to admission selection, elderly patients are more likely to be denied ICU admission, due to comorbidities and reduced life expectancy [18]. However, age difference was particularly striking in the first quartile of age distribution, at 42 years for patients admitted to ICU vs 51 years old for those non admitted to ICU IE patients in this study, while there was no significant difference in the proportion of ICU admission among elderly patients. Of note, we previously showed that headache was more frequent in younger patients with IE [15], which may be related to higher intra-cranial pressure during IE in this population with a lower prevalence of baseline brain atrophy.

With advances in the epidemiology of IE, improved tools for microbiological diagnosis, and dramatic progress in the diagnosis of auto-immune IE [19], a causative agent could be identified in 70% of IE patients who required ICU admission. Of note, the French guidelines advocate for early empirical treatment with high-dose intravenous acyclovir and amoxicillin [14], which was appropriate in 104/137 (76%) ICU patients with documented IE. Our study also highlights the benefit of comprehensive aetiological investigation, since for up to 92% of IE with identified causative agent, a specific anti-infective treatment was indicated.

Only 45% of patients were categorized as good outcome, with good recovery at hospital discharge. This is in line with a previous study on HSV IE admitted in the ICU, where up to 71% of patients had poor functional outcome, including 17% lethality at 90 days [7]. We found no association between HSV IE and outcome in multivariate

analysis. This may be related to the strong recommendation for prompt initiation of high-dose intravenous acyclovir in patients with suspected IE [20]. By contrast, acyclovir treatment started later than 2 days after symptoms onset was independently associated with poor outcome, suggesting only HSV patients with a late treatment are at risk of poor outcome. As 2 days was also the median delay between symptoms onset and hospitalization in our cohort, this outlines how important is the early start of acyclovir on admission of patients with suspected IE, especially in those who require ICU.

Abnormal brain imaging abnormalities have previously been associated with poor outcome [8]. Conversely, low CSF white cells count has not, to our knowledge, been reported as an independent risk factor for poor prognosis in IE. However, low CSF white cells count is an independent predictor of poor outcomes in bacterial meningitis [21]. Early-onset status epilepticus has been associated with poor outcome in several cohorts [3,22], but we did not confirm such association in ICU patients, as was also the case for other factors, such as coma on admission or infratentorial neurological signs. However, coma on admission was associated with death in the whole ENCEIF cohort [15], and with poor prognosis in another study [9]. When focusing only on critically ill patients, with nearly 20% of IE presenting with coma on admission, sometimes reversible while treating status epilepticus, impact of coma seems not associated with outcome, as other clinical symptoms such as motor deficit and supratentorial signs are independently associated with functional status at hospital discharge. The high prevalence of severe deficit at discharge advocates for appropriate rehabilitation programs. Indeed, less than half of all patients mechanically ventilated for more than 24 h are alive and free of new disability 6 months after ICU admission [23], with potential severe disabilities, including critical illness polyneuropathy [24]. A large proportion of IE survivors suffer from sequelae which advocate for neuropsychological rehabilitation programs whenever needed [25,26]. These findings support the need to add the frailty scale [27] to the clinical assessment in IE patients before ICU admission.

Our study has several limitations. First, despite the large sample size, and the multicentre design, our findings may not apply to other countries with different health care system, and different epidemiology. Second, we were unable to report data on outcome following hospital discharge, due to a large proportion of missing data. Third, because the ENCEIF cohort was not designed as an ICU cohort, we did not have data on several ICU items, such as SOFA score or organ dysfunction, which could have been of interest to ICU physicians. Fourth, as we had no data on previous brain imaging in patients enrolled in the cohort, we can not differentiate brain imaging lesions associated with IE from pre-existing lesions. However, our study has strengths, including the standardized prospective collection of data, the large sample size, the temporal association with the publication of national guidelines, and the involvement of a large consortium of physicians with interest in the field of IE.

Conclusion

HSV is the primary cause of IE requiring ICU admission. Prompt acyclovir initiation is essential, as time from symptoms onset to acyclovir start >2 days is associated with poor outcome. IE patients admitted in ICU have a poor prognosis with 11% rate of in-hospital mortality and 15% prevalence of severe disabilities in survivors at discharge.

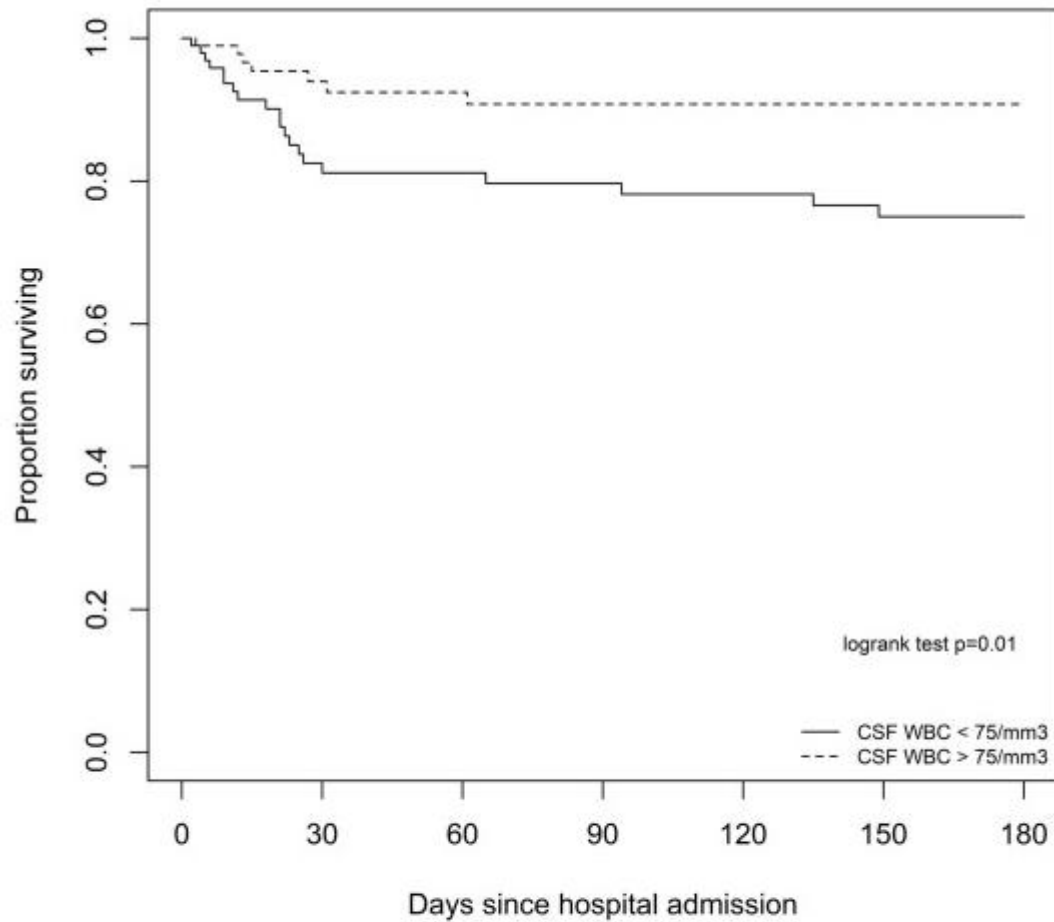
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Figure 1. Kaplan Meier survival curve until 180 days among patients with high and low cerebrospinal fluid white cells count

Footnote: CSF WBC: cerebrospinal fluid white blood cells



	number at risk						
	0	30	60	90	120	150	180
high CSF WBC	96	63	57	52	51	51	46
low CSF WBC	97	61	55	53	50	48	46

Table 1. Comparison between intensive care unit (ICU), and non-ICU patients with infectious encephalitis

Variables	No ICU admission (n=288)	ICU admission (n=198)	P-value
Demographics, comorbidities			
Age, years	67 [51-75]	63 [42-74]	0.032
Male gender	173 (60.3)	125 (63.1)	0.59
Diabetes	41 (14.3)	26 (13.2)	0.836
Solid Cancer	20 (7.0)	19 (9.6)	0.394
Haematological malignancies	16 (5.6)	9 (4.6)	0.758
Immunodeficiency	38 (13.2)	18 (9.1)	0.212
Underlying neurological disease	18 (6.4)	11 (5.6)	0.86
Autonomy prior to encephalitis	272/285 (95.4%)	186/195 (95.4)	1
Causes of infectious encephalitis			
Herpes simplex virus	57 (19.8)	72 (36.4)	<0.001
Varicella-zona virus	45 (15.6)	20 (10.1)	0.105
<i>Mycobacterium tuberculosis</i>	4 (1.4)	7 (3.5)	0.132
<i>Listeria monocytogenes</i>	10 (3.5)	12 (6.1)	0.189
Arboviruses	30 (10.4)	4 (2.0)	<0.001
- Tick borne encephalitis	24 (8.3)	1 (0.5)	<0.001
Enterovirus	3 (1.0)	3 (1.5)	0.691
Influenza virus	3 (1.0)	7 (3.5)	0.099
Miscellaneous *	29 (10)	12 (6)	0.118
Unknown aetiology	107 (37.2)	61 (30.8)	0.178

ICU: intensive care unit. Qualitative data are expressed as n (%), quantitative data as medians [interquartile range]

* Epstein-Barr virus (n=6), *Mycoplasma* sp. (n=4), *Cryptococcus neoformans* (n=4), JC virus (n=3), measles (n=3), *Borrelia burgdorferi* (n=3), human herpesvirus 6 (n=2), *Capnocytophaga canimorsus* (n=2), *Tropheryma whipplei* (n=2), *Leptospira* sp. (n=2), cytomegalovirus, primary HIV infection, Parvovirus B19, *Rickettsia* sp., *Legionella pneumophila*, *Francisella tularensis*, *Bartonella henselae*, *Coxiella burnettii*, *Treponema pallidum*, *Anaplasma* sp. (one patient each)

Table 2. Comparison of infectious encephalitis with good outcome, and poor outcome, in patients who required intensive care unit admission: characteristics

Variables	All patients admitted in intensive care unit n=198	GOS on discharge, 4-5 n=146	GOS on discharge 1-3 n=52	P
Clinical (n, %)				
Headhache	81 (40.9)	61 (41.8)	20 (38.5)	0.8
Confusion	126 (63.6)	91 (62.3)	35 (67.3)	0.636
Impaired consciousness	109 (55.1)	81 (55.5)	28 (53.8)	0.967
Coma	35 (17.7)	23 (15.8)	12 (23.1)	0.329
Seizure	49 (24.7)	39 (26.7)	10 (19.2)	0.375
Supratentorial focal signs	68 (34.3)	42 (28.8)	26 (50.0)	0.009
- Aphasia	54 (27.3)	35 (24.0)	19 (36.5)	0.117
- Deficit (motor/sensitive)	22 (11.1)	11 (7.5)	11 (21.2)	0.015
Infratentorial focal signs	18 (9.1)	13 (8.9)	5 (9.6)	1
- Cranial nerve paralysis	10 (5.1)	5 (3.4)	5 (9.6)	0.167
- Cerebellar syndrome	8 (4.0)	8 (5.5)	0 (0.0)	0.189
Fever	163 (82.3)	119 (81.5)	44 (84.6)	0.77
Skin rash	14 (7.1)	10 (6.8)	4 (7.7)	1
Respiratory symptoms	28 (14.1)	15 (10.3)	13 (25.0)	0.017
Investigations				
CSF erythrocytes, /mm ³ *	24.50 [4.00, 170.75]	27.50 [7.00, 170.25]	11.00 [1.00, 258.75]	0.108
CSF white cells, /mm ³	74.00 [20.00, 252.00]	103.00 [24.50, 349.00]	30.50 [9.25, 150.75]	0.006
CSF protein, g/L	0.93 [0.59, 1.62]	0.87 [0.59, 1.52]	1.00 [0.59, 2.21]	0.429
CSF lactates, mmol/L *	2.91 [2.28, 3.63]	2.91 [2.30, 3.60]	3.02 [2.20, 4.04]	0.958
Abnormal EEG *	129 (79.1)	90 (76.9)	39 (84.8)	0.37
Abnormal brain imaging	127 (64.1)	83 (56.8)	44 (84.6)	<0.001
Cause of encephalitis				
- Unknown	61 (30.8)	54 (37.0)	7 (13.5)	
- Other agents	65 (32.8)	48 (32.9)	17 (32.7)	
- HSV	72 (36.4)	44 (30.1)	28 (53.8)	0.002

Qualitative data are expressed as n (%), quantitative data as medians [interquartile range]

GOS: Glasgow outcome scale, CSF: Cerebrospinal fluid; EEG: electroencephalogram

*missing data \leq 10%, except for CSF lactates (n=113), CSF red cells count (n=36), and electroencephalogram (n=35)

Table 3. Comparison of infectious encephalitis with good outcome, and poor outcome, in patients who required intensive care unit admission: management, and complication

Variables	Missing data	All patients admitted in intensive care unit n=198	GOS on discharge, 4-5 n=146	GOS on discharge 1-3 n=52	<i>P</i>
Intravenous acyclovir	7	180/191 (94)	133/141 (94)	47/50 (94)	1.0
Time from symptoms onset to acyclovir start, days	20	2.00 [1.00, 5.00]	2.00 [1.00, 4.00]	3.00 [2.00, 6.00]	0.029
Time from hospitalization to acyclovir start, days	20	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	1.00 [0.00, 2.00]	<0.001
Acyclovir dose	29				0.902
- 10 mg/kg/8 h		130 (66)	97 (66)	33 (64)	
- ≥15 mg/kg/8 h		39 (19)	28 (19)	11 (21)	
Mechanical ventilation	1	111/197 (56)	68/145 (47)	43/52 (83)	<0.001
- For neurological failure	0	102 (52)	65 (45)	37 (71)	0.002
- For respiratory failure	0	27 (14)	11 (8)	16 (31)	<0.001
Length of mechanical ventilation, days	10	7.00 [4.00, 14.00]	6.00 [3.00, 9.00]	8.50 [6.00, 20.50]	0.004
- among survivors	8	6.00 [4.00, 12.00]	6.00 [3.00, 9.00]	9.00 [6.00, 33.00]	<0.001
Use of vasopressor	17	45/181 (25)	22/138 (16)	23/43 (51)	<0.001
- duration, days	8	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]	3.00 [1.25, 4.00]	0.299
Coma	12	78/186 (42)	47/137 (34)	31/49 (63)	<0.001
Lowest Glasgow coma score	12	11 [8, 14]	12 [8, 14]	9 [6, 13]	0.007
Seizure	6	73/192 (37)	55/143 (38)	18/49 (37)	0.351
- status epilepticus		26/73 (32)	16/55 (29)	10/18 (56)	0.052
In ICU-acquired infection, n (per 1000 patient-days at risk)	1	58 (25.5)	31 (26.4)	27 (24.4)	0.763
ICU LOS, days	18	6.00 [4.00, 14.00]	5.00 [3.00, 10.25]	12.00 [6.00, 23.50]	<0.001
Hospital LOS, days	0	25.00 [16, 38.75]	23.0 [16.0, 36.75]	32.00 [16.75, 49.5]	<0.001

ICU: intensive care unit, LOS: length of stay, GOS: Glasgow outcome scale.

Qualitative data are expressed as n (%), quantitative data as medians [interquartile range]

Table 4. Risk factor for poor outcome at hospital discharge (Glasgow outcome scale ≤ 3), multivariate analysis (Goodness of fit: $P=.95$)

Variables	Bêta	Odds Ratio	Confidence interval [95%]	P
Immunodeficiency	1.45	4.24	[1.15 – 15.60]	0.030
Supratentorial focal signs on admission	0.96	2.60	[1.15 – 5.84]	0.021
CSF white cells count $< 75/\text{mm}^3$	1.59	4.92	[2.11 – 11.45]	<0.001
Abnormal brain imaging	1.77	5.82	[2.15 – 15.81]	<0.001
Time from symptoms onset to acyclovir start >2 days	1.21	3.35	[1.27 – 8.87]	0.015

CSF: cerebrospinal fluid